ISO/TC 84/WG 3 ad hoc 5

N14

Needle-free injectors for medical use

Convenor: **Paul E. Jansen, USA**
Secretary: **Bibi Nellemose, Denmark**

November 1999

R E P O R T

of the 2nd meeting of ISO/TC 84/WG3 ad hoc 5 in Minneapolis, Minnesota, USA

on 19, 20 and 21 October 1999

LIST OF EXPERTS PRESENT AT THE 2nd MEETING OF
ISO/TC 84/WG 3/ ad hoc 5 "Needle-free injectors"

COUNTRY	NAME	NOMINATED BY
Denmark	Jørn Rex	DS
Sweden	Bohdan Pavlu	SIS-HHS
USA	Harold Yeager	ANSI
	Paul E. Jansen	ANSI, Convenor
	Peggy Holland	Invited
	Linda D'Antonio	Invited
	Michael Roy	Invited
	Antonio A. Bendek	(replacing Lucio Gambattista)
	Samuel B. Nickerson	Invited
United Kingdom	Richard Hall	Invited
Denmark	Bibi Nellemose	Secretariat

1. Opening of the meeting

The convenor, Paul E. Jansen, welcomed the experts to the meeting and thanked Medi-Ject Corporation for hosting the meeting.

Medi-Ject gave a short presentation of their company and their products. They showed their new product the “Vision” injector, which gives 3,000 shots and costs 29 cents per shot. The pharmaceutical industry is investing in inhalators as a substitute to pen-injectors, but it was underlined that jet injection is the most advantageous solution since nobody is happy about using needles. Therefore most people - especially children - want to use pressure injectors, which are seen as the preferred means of parenteral drug delivery.

2. Roll call of experts

The experts present and listed in this report presented themselves.

3. Approval of the agenda

The draft agenda was approved.

4. Pharmacokinetics - Liquid applications (N8)

David L. Bremseth, Medi-Ject Corporation, presented a view of what they had experienced working with liquid applications. Peggy said that the group should keep in mind that there are different kinds of molecules, and that it therefore might be suitable to deal with this in a more general way.

Paul said that it would be very difficult not to have something in the standard about data and a number of ways to find it. The purpose is to provide a guideline for the company which will start to produce needle-free injectors.
Furthermore, he did not see the significant differentiating features of liquid and powder injection complicating the standard. The basic principle is pretty much the same.

The issues may not be different when dealing with needle-free injectors. When preparing the standard, the group should keep in mind what the counterpart is doing.

5. Pharmacokinetics - Powder applications (N9)

Richard Hall informed of the needle-free powder injection system by PowderJect Technologies Ltd. Paul kindly asked Richard not only to cover the industry as is today but try to explain what will happen in future also.

Richard informed the group that PowderJect works with the pharmaceutical suppliers to develop a system for powder applications. The company intends to produce both single-use disposable and re-usable delivery systems.

There are two ways of delivering the drug:

- Dermal delivery
- Muscosal delivery

For powder delivery, velocity shall be sufficient to penetrate the skin. PowderJect is trying to characterize the process powder penetration into the skin. For the process to be successful the correct combination of particle velocity and particle mass is required.
Gas dynamics and particle character control the depth of delivery of the drug into the skin.

Jørn asked what the tolerance is in terms of particle size and Richard replied that a typical particle size fraction might be 25 and 55 microns. The drug is formulated as a fine powder and the specification of the powder is very important when dealing with the powder delivery.

The depth of penetration is dependent on a number of factors; particle size, mass, shape and surface condition; particle velocity; skin condition and thickness. Particle size range is dependent on the application but can vary between as much as 2um (gold) and 70um (drug). PowderJect actually controls the reformulation of the particles.

Michael asked how many decibels the health care personnel can be exposed to. Richard indicated that PowderJect products produced sound levels well within currently recognized safety levels and sound levels which were also subjectively acceptable to users. Paul replied that from a standards perspective, they should be taking this issue into consideration.

The question about interchangeability was raised. Would it be suitable for the patient to use a powder from one company and a device from another company? Jørn asked whether PowderJect sees free interchangeability as a dream rather than reality. Richard's response was in two parts: 1) He stated that PowderJect has established a unique technology and has protected this position and will continue to do so by management of IPR. The company is creating a brand which will provide income to the company and shareholders. In the event that interchangeability could impact adversely on income generation it would not be acceptable to PowderJect. 2) His personal view was that after a number of years (many) it might be in PowderJect's interest to accept some degree of interchangeability but only when the market had matured and benefits would accrue to the company resulting from a change in strategy.

However, there was further discussion within the meeting which concluded that this seems to be a fundamental barrier. From a patients perspective, it would be most appropriate if each individual patient could buy drug from a company and use it with any device of any origin. Compared to film industry - the customers can buy a film for their camera and it fits and works no matter which type of camera they have. Richard stated that the complexity of the PowderJect drug-device system in terms of the match of particle to device technology meant that it would be very challenging to achieve the level of interchangeability that patients (and regulators) might want even if PowderJect agreed to allow it.

The group discussed tolerance in relation to powder applications. The pain tolerance is at a minimum - the patient cannot feel the injection. Richard confirmed that a PowderJect administration is pain-free.

In relation to the clinical work, the powder applications have been clinically tested in Phase I and Phase II trials in more that 150 patients with excellent results. No unacceptable skin responses were found. Richard stated that PowderJect's objective in addition to proving efficacious delivery of drugs and vaccines was "to do no harm".

Paul asked Richard what PowderJect does with the physical hardware to see whether the dose has been delivered, to which Richard replied that they considered the particles themselves and what happened when penetrating the skin. They seek to establish where the particles have gone and what has actually been delivered into the skin. Filter papers could be used as an impact target to collect drug to establish data on the delivery and silicone materials, for example, were used for the purposes of penetration modelling in vitro .

Michael informed the group that in the field of vaccines, the comparison of what happens using pig's skin is very similar to human skin. This is tested at every stage imaginable - at every test point, time point etc. So validation is becoming more reliable now, since a lot of tests have been performed and data reviewed.

Paul said that the challenge in finding the dose accuracy with the pen injectors was easy. The patient could just set the dose and then see the accuracy. With this it is a little more complicated since we do not know exactly how much of the drug is penetrating the skin. We can measure what comes out of the apparatus, but we will have to measure how much is actually penetrating the skin and assimilated in the body.

Jørn asked Richard whether their products are fixed dose or multiple dose devices. Richard replied that they produce fixed dose devices, and that they are considering applications which will require multiple fixed doses from a re-usable device.

Jørn expressed that he saw this as a rather expensive method. Michael said that the vaccine market is the same as this field. He was of the opinion that people who are suffering from such a desease like diabetes are willing to pay what it costs to avoid the pain. Furthermore, the needle-free pen injectors make it much easier for the patient to take the drug.

Moreover, the group decided that drug residue needs to be some part of the standard being an important issue also.

6. Hybrid Technologies

General discussion:
Paul asked for an open discussion. How can we make it easier to make flow through the skin?
- And should pressure and time be included in the standard?

Paul said that the group should consider what it is aiming at. Bohdan said that the group should make a standard on a system which is needle-free. Even though a system has a very small needle it should not be considered as being needle-free. Paul asked whether a device with a needle not penetrating the skin could be included under needle-free pen injectors. Jørn replied that in his opinion also a tiny needle still is a needle. Having a very small needle is not a needle-free device.

The scope agreed on at the last meeting was slightly changed as follows:

Draft scope:

> This international standard specifies performance requirements and test methods for all needle-free injectors which actively force the medicinal product to penetrate the skin or mucosal membranes without any part of the device penetrating the membrane.
>
> The standard covers devices intended for human use in clinics and for personal use.
>
> The injection process does not include passive delivery methods such as sprays, inhalers, patches, liquid drops, ultrasonics, transdermal and infusion systems.

The members will comment on the draft scope before next meeting.

7. PATH Testing - Review of Tests (N 10)

PATH - Programme for Appropriate Technology in Health (a non-profit organization).

Maggie Holland, Medi-Ject Corporation, presented the PATH testing system which objective is to compare different devices - how is one performing compared to other devices?

There are two steps in the PATH test programmes. The first is to test the products - by the force test and penetration test - to measure changes during the course of a single injection. The second step is to validate the test.

There are two types of test:

1) The force test measures changes during the course of a single injection and can see if one injector has higher or lower pressures than another device.

2) The penetration test in which the device is shot through consistent medium with consistent backing. The result is observed to find out whether there is still liquid on the surface and hole in the skin material.

However, there are some disadvantages when performing these tests since the material used for the testing has different properties than human skin and the potential problems as bleeding and pain are not considered during the tests.

Michael was of the opinion that these tests - which in theory are very good - will be too difficult to use when standardizing since they are not reliable enough for that purpose. They cannot reliably predict which device will be clinically successful.

Summary:

Although both penetration testing and jet force testing can be useful tools in helping to understand jet injectors, they have not been developed to the point that they can predict success in the field. Without some bridge to clinical data, data gathered from the tests should be used with care, especially when comparing dissimilar types of jet injectors (i.e., injectors with different power sources and force profiles.

8. Review Indianapolis Meeting

Peggy informed the other members of the group that the report of the FDA meeting which recently took place in Washington on needle-free injectors could be downloaded from the following web address:

http://www.cdc.gov/nip/dev/jetinject.htm

Linda informed that FDA is preparing a new draft for a guidance document on needle-free injectors, and is in this connection trying to get some input from the industry.

Peggy added that the objective from the FDA's point of view is that a company can perform the test on their device and meeting the requirements of the guidance document. It makes the process much quicker. The preliminary scope is shown in their minutes (cf. the web address above) and they are very interested in the ad hoc 5 group.

It was decided that Peggy should contact FDA.

Peggy asked whether the group should develop a standard for both device and drug - or only the device to which Paul replied that the standard may simply provide some kind of data.

Paul explained the difference between horizontal and vertical standards. The horizontal standards are basic standards describing the overall picture of a certain issue - an example is the standard on SI units. The vertical standard - on the other hand - describes a certain subject in much more detail.

Hal handed out a paper listing the major categories which might be advantageous to include in the standard. The group went through the document. Hal stressed that it was only a document with ideas to include in the standard - like a brainstorm document (N11).

I Safety
The group discussed whether “biocompatibility” should be included in the standard. This is dealt with in ISO 10993. The group decided to leave safety as it is for now and then get back to the issue when preparing the standard.

II Preconditioning/Testing
Free fall with an empty device was discussed whether it should be included or not. Dealt with in ISO FDIS 11608-1.

It was decided to include dry-firing into the standard. If the patient fires the device and is convinced that the device has been fired properly, it should be dealt with under safety.

The group agreed that clinical data is a very important issue - it was also the biggest item which was discussed in Indianapolis.

It was discussed whether test methods should be part of the standard. The group decided not to include the issue in the first place and then discuss it again when having prepared a first draft.

III Scientific Understanding
Hal said that he did not know whether any of these terms under "Scientific understanding" should be mentioned in the standard, but the group would have to take the issues into consideration anyway when preparing the standard. The section is just mentioned in this document to provoke a discussion.

IV Labelling
The group discussed whether this issue should be included in the standard, or if there should just be a reference to other standards dealing with this task. Paul added that if regulation changes it will affect the ISO standards accordingly.

V Product Options
It was discussed whether the group should be dealing with single-dose or multi-dose devices, various filling methods, consumer products etc.

VI User Interactions
The group discussed whether contact pressure with skin should be included in the standard.

The group prepared some definitions for the standard. Linda will send the definitions to DS, which will prepare the first draft when all contributions are received.

Dose accuracy:
The group discussed dose accuracy. In the pen injector series real basic statistics are given. The question was raised whether it would be sufficient just to fire the injector and then measure. David L. Bremseth said that the way they measure dose accuracy at Medi-Ject, is to fire the jet injector and then measure the drug coming out - not to measure the drug penetrating the skin.

Dose accuracy is the dose coming out of the injector. This is not an operator dependent process. Hal mentioned that the group would have to define the energy required to expel the dose.

Bohdan mentioned that the group should take into consideration that there are several ways of determining the dose accuracy. There is the dose accuracy into the injector and the dose accuracy coming out of the injector. Furthermore, there is the dose accuracy when the patient fills the device and when it is fired.

Conclusion:

Paul concluded from the discussion that the following are important issues in the process:

1) To make a measurement on what is expelled - do you expel from the device what you come into it?

2) To make some requirements via a model on some kind of a non-invasive, non-clinical methodology which every injector must fulfil to comply with the standard.

3) To develop an in vitro test method.

David L. Bremseth mentioned that Medi-Ject takes each and every of their models/designs to a clinic for testing to be sure that they have the right measures. Jørn did not understand why Medi-Ject makes the dose accuracy testing in a clinic, since dose accuracy - in his opinion - is measured on what goes into the patient and not based on the device.

Paul said that the group should try to close the gap, to see what and how to measure. In relation to insulin, it has a potential dose requirement. The group should try to define the most appropriate method to make the patients feel safe in relation to which dose they are supposed to have. Thereby, it is more important what comes into the body. Linda added that it is commonly known that with too low pressure, the drug does not penetrate the surface, so the group will have to define the pressure also.

Hal reminded the group that the purpose of this work is not to test all devices. It is a technical question of how you need to do it. Paul added that the group should pretend being a new company designing a new product. We are trying to see what is necessary to be useful for the industry. We are on the inside track.

The group made a list of factors relating to dose accuracy:

Powder system	Liquid system
• loading process • energy • pressure vs. time	• loading process • energy • expelling process

• particle velocity	

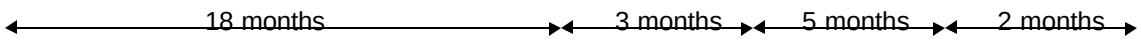
Bohdan mentioned mechanical dosing versus the actual dose. If we just play with the idea to make dose accuracy - we should look at how the dose is delivered. Maybe the two things should be divided.

Jørn supported this idea - to start with the question of how to test. In his opinion, it would be most logical to discuss the test method first and thereafter get to the accuracy issue. A special methodology should be established and then figure out how to measure it.
Paul tended more to go with the idea of defining the accuracy and then go for the other.

Project Plan

Bibi explained the stages in the process of preparing a standard.

ISO standards process



Stage 0	Stage 1 NP	Stage 2 WD	Stage 3 CD	Stage 4 DIS	Stage 5 FDIS	Stage 6 ISO
Preliminary work	New work item/Draft documents	Working Draft	Committee Draft	Draft International Standard	Final Draft International Standard	Publication

Stages:

Stage 0: Preliminary work item stage (PWI). No time limit.
Stage 1: Proposal stage. New work item proposal (NP). A proposal for a new work is circulated for a 3 month vote.
Stage 2: Preparatory stage. Working drafts (WD).
Stage 3: Committee stage. Committee draft (CD). A CD is circulated for a 3 month vote by participating members of the technical committee. Comments allowed.
Stage 4: Enquiry stage. Draft International Standard (DIS). The DIS is circulated for a 5 month vote by all members of ISO. Comments allowed.
Stage 5: Approval stage. Final Draft International Standard (FDIS). The FDIS is circulated for a 2 month vote by all members of ISO. No comments allowed - only Yes/No.
Stage 6: Publication stage. The document is published as an International Standard.

ISO recommends that a standard is prepared within a period of 3 years. Paul asked the group about their opinion on this ISO schedule for preparing a standard. Peggy asked for the reason why it

took WG3 7 years to prepare the standard on pen injectors. Paul replied that a lot of politics was implied in this standard, which was why it took so long. Furthermore, ISO has revised their schedule for the preparation of standards and has thereby limited the process to 3 years.

Paul was of the opinion that the group would be able to prepare this standard within the above mentioned time frame of 3 years.

Action: The DS secretariat and Paul will get back to the matter in relation to the approval of the NWIP.

The group prepared a project plan with the purpose of organizing the work and settling the target dates for the various stages of the work: *(see next page)*

Period	Target	Action
November 1999 - December 1999	Preliminary document	ad hoc 5
December 1999 - 28 February 2000	Review/comments	ad hoc 5 DS secretariat
28 February 2000	Meeting in London in connection with the conference on Needle-free injectors.	ad hoc 5
March 2000	1st Working Draft (WD). **Milestone 1**	DS secretariat
May 2000	Meeting in Stockholm 15 to 19 May. Finalize WD. **Milestone 2**	ad hoc 5 DS secretariat
August 2000	The WD is sent to the ISO/TC 84 secretariat for submission as CD (stage 3).	DS secretariat
October 2000	The CD is submitted by the TC for a period of 3 months. (October 2000 - January 2001)	ISO/TC 84 sec.
January 2001	ISO/CD with comments. **Milestone 3** ISO/TC 84 makes a compilation of comments received on the CD. The comments are sent to the DS secretariat for further progress.	ISO/TC 84 sec.
February 2001	US meeting to incorporate the comments received on CD level. Preparing the DIS. The document is thereafter sent for translation into French.	ad hoc 5 DS secretariat
June 2001	French version is finalized. Both documents (E+F) are sent to the ISO/TC 84 secretariat for initiating stage 4 - the submission of the ISO/DIS.	DS secretariat
August 2001	ISO submits the ISO/DIS for a period of 5 months. (Enquiry). (August 2001 to January 2002). **Milestone 4**	ISO/CS
February 2002	The group meets to incorporate the comments received during enquiry - preparing the ISO/FDIS	ad hoc 5 DS secretariat
March 2002	The French version of the document shall be corrected according to the updated English version, and the documents will be sent to the ISO/TC 84 secretariat for initiating stage 5 (ISO/FDIS).	DS secretariat ISO/TC 84 sec.
May 2002	The ISO/FDIS will be submitted by ISO to all ISO members for a 2 months vote (Yes/No). **Milestone 5**	

September 2002:	Published as an ISO standard. **Milestone 6**	ISO/CS

Official target dates for finalizing the work of ad hoc 5 - will be transferred to ISO/TC 84 secretariat:

Stage 2 - WD:	2000-08
Stage 3 - CD:	2000-10
Stage 4 - DIS:	2001-08
Stage 5 - FDIS:	2002-05
Stage 6 - ISO:	2002-09

Paul presented the time schedule for the group, and informed at the same time that DS is considering to take over the ISO/TC 84 secretariat, since Ms. Sancho from AFNOR (France), wants to resign. Paul said that it would be advantageous for the group having DS to take over this task, since it would make the flow between the TC and this ad hoc group much easier and time-saving.

In relation to the funding of the work of the ISO/TC 84 secretariat and the ad hoc group, DS presented a budget indicating the costs for the administration of the secretariats for the coming year. To be able to fulfil the administrative work, DS asked the group whether it would be possible for them to provide part of the funds for the administrative work. If no financial support is granted in this field, DS will - unfortunately - not be able to continue as secretariat for the group.

The group was positive to the thought of providing financial support to DS for the administration of the secretariats and the budget was approved. However, the DS secretariat underlines that the experts are not bound to pay the administration costs. The grants are considered as a financial support to DS which is necessary for administrating a secretariat.

Linda D'Antonio said that she would face difficulties in funding the work since her company is a very small company with only 8 employees. However, she said that they would be able to contribute with a small amount.

The group agreed on providing financial support to DS and made a proposal for dividing the administration costs:

Administration costs:

1 - 10 people	500 USD/year
11 -100 people	2,000 USD/year
101 - 1000 people	4,000 USD/year
> 1000 people	10,000 USD/year

It was decided to go for a 3 year commitment with annually renewal.

Furthermore, it was decided that DS will invoice the amounts by December 1999 to fall due January 2000, so that the administration costs follow the calendar year. Furthermore, DS shall contact the experts not present to inform them accordingly.

9. Standards Workshops

The group split into discussion groups for the afternoon session on the 2nd meeting day. Some definitions for the standard were prepared by one of the two groups. Linda will send the definitions to DS, which will prepare the first draft when all contributions are received. Linda made meeting notes on this session cf. N12.

10. Date and place of next meeting

The next meeting of the group was scheduled to take place 1st and 2nd March 2000 at BSI in London, in connection with the conference on needle-free injectors. DS will contact BSI to arrange for meeting facilities.

® DS has arranged for meeting room 311 at BSI from 9.00 am both days - address and further information will follow with the invitation to the meeting.

16 and 17 May 2000 the group will meet in Stockholm hosted by Bohdan Pavlu.

11. Any other business

No items to be discussed.

Paul closed the meeting by thanking Medi-Ject once more for hosting the meeting. Furthermore, he informed the group that it might be advantageous to have a user-group represented to avoid just having the manufacturers represented in the group. It was agreed that Paul would pursue this.

Paul expressed his satisfaction with the work done during this meeting.